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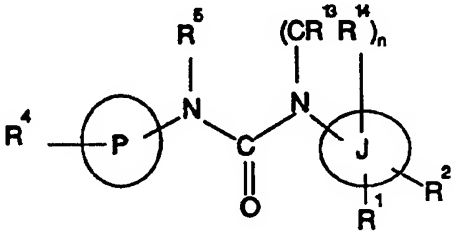
(54) Title: TRICYCLIC DERIVATIVES AS $5HT_{2C}$ AND $5HT_{2B}$ ANTAGONISTS

(57) Abstract

Compounds of formula (I), processes for their preparation and their use as CNS agents are disclosed. In said formula P represents phenyl, a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur; J represents a bicyclic aromatic or partially saturated ring system; $R^1$ and $R^2$ are independently hydrogen, halogen, hydroxy, oxygen or $C_{1-6}$alkyl optionally substituted by one or more halogen atoms; $R^4$ is hydrogen, $C_{1-6}$alkyl, $C_{1-6}$alkylthio, halogen, nitro, cyano, $CF_3$, $NR^8R^9$, $CO_2R^{12}$, $CONR^{12}$ or $OR^{12}$, where $R^8$, $R^9$ and $R^{12}$ are independently hydrogen, $C_{1-6}$alkyl or aryl$C_{1-6}$alkyl; $R^5$ is hydrogen or $C_{1-6}$alkyl; n is 2 or 3; and the groups $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$alkyl, provided that: P is not a heterocyclic group when J forms a benzothiophene ring.

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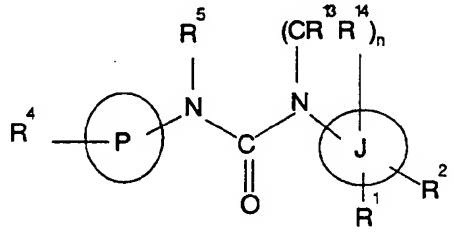
# TRICYCLIC DERIVATIVES AS 5HT2C AND 5HT2B ANTAGONISTS

This invention relates to compounds having pharmacological activity, to a process for their preparation, to compositions containing them and to their use in the treatment of mammals.

WO 94/04533 (SmithKline Beecham plc) describes indole and indoline derivatives which are described as possessing $5HT_{2C}$ receptor antagonist activity. A structurally distinct class of compounds has now been discovered, which have been found to have $5HT_{2C}$ receptor antagonist activity. Some or all of the compounds of the invention also exhibit $5HT_{2B}$ antagonist activity. $5HT_{2C/2B}$ receptor antagonists are believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS as well as microvascular diseases such as macular oedema and retinopathy.

Accordingly, in a first aspect, the present invention provides a compound of formula (I) or a salt thereof:



(I)

wherein:

P represents phenyl, a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

J represents a bicyclic aromatic or partially saturated aromatic ring system;

$R^1$ and $R^2$ are independently hydrogen, halogen, hydroxy, oxygen, or $C_{1-6}$ alkyl optionally substituted by one or more halogen atoms;

$R^4$ is hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkylthio, halogen, nitro, cyano, $CF_3$, $NR^8R^9$, $CO_2R^{12}$, $CONR^{12}$ or $OR^{12}$, where $R^8$, $R^9$ and $R^{12}$ are independently hydrogen, $C_{1-6}$ alkyl or aryl$C_{1-6}$alkyl;

$R^5$ is hydrogen or $C_{1-6}$ alkyl;
n is 2 or 3; and
the groups $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl,
provided that:
P is not a heterocyclic group when J forms a benzothiophene ring.

$C_{1-6}$ alkyl groups, whether alone or as part of another group, can be straight chain or branched and are preferably $C_{1-3}$ alkyl, such as methyl, ethyl, n- and iso- propyl.

Suitably$R^1$ and $R^2$ are independently hydrogen, halogen, hydroxy, oxygen, or $C_{1-6}$ alkyl optionally substituted by one or more halogen atoms. Preferably $R^1$ and $R^2$ are both hydrogen.

Suitably $R^4$ is hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkylthio, halogen, $CF_3$, $NR^8R^9$ or $OR^{12}$, where $R^8$, $R^9$ and $R^{12}$ are independently hydrogen, $C_{1-6}$ alkyl or aryl$C_{1-6}$alkyl. Preferably $R^4$ is hydrogen.

Suitably $R^5$ is hydrogen or $C_{1-6}$ alkyl. Preferably $R^5$ is hydrogen.

Suitably P represents phenyl, a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur. Suitable moieties when the ring P is a 5-membered aromatic heterocyclic ring include, for example, isothiazolyl, isoxazolyl, thiadiazolyl and triazolyl. Suitable moieties when the ring P is a 6-membered aromatic heterocyclic ring include, for example, pyridyl, pyrimidyl or pyrazinyl. When P is a quinoline or isoquinoline residue, the urea moiety can be attached at any position of the ring, preferably to the 4-position. Preferably P is a 6-membered heterocyclic ring, most preferably a 3-pyridyl group.

The urea moiety can be attached to a carbon or any available nitrogen atom of the ring P, preferably it is attached to a carbon atom.

Suitably J represents a bicyclic aromatic or partially saturated ring system. Preferably J represents a quinoline, tetrahydroquinoline, indazole, benzothiophene, dihydrobenzothiophene, indene, indane, benzothiazole, benzofuran or dihydrobenzofuran ring. Preferably J is quinoline, tetrahydroquinoline, benzothiophene, benzofuran or indane.

Suitably the group $-(CR^{13}R^{14})_n-$ forms an ethylene or propylene group each of which can be substituted by $C_{1-6}$alkyl. When J is quinoline or tetrahydroquinoline the group $-(CR^{13}R^{14})_n-$ can be attached to the 5- or 7-positions of the ring J, with the urea linkage attached to the 6-position. When J is quinoline the group $-(CR^{13}R^{14})_n-$ can also be attached to the 2- or 4-positions of the ring J, with the urea linkage attached to the 3-position. When J is a 6,5 ring system, for example a benzofuran ring, the group

-$(CR^{13}R^{14})_n$- can be attached to the 4- or 6-positions, with the urea linkage attached to the 5-position, or -$(CR^{13}R^{14})_n$- can be attached to the 5- or 7-positions, with the urea linkage attached to the 6-position. Preferably the group -$(CR^{13}R^{14})_n$- is ethylene.

Particularly preferred compounds of formula (I) include:

1-(3-Pyridylcarbamoyl)-2,3-dihydro-1H-pyrrolo [2,3-g] quinoline,
2-Methyl-6,7-dihydro-5-(3-pyridylcarbamoyl)-furo[2,3-f]indole,
1-(3-Pyridylcarbamoyl)-2,3-dihydropyrrolo-[2,3-f]-indene,
2,3-Dihydro-1-(3-pyridylcarbamoyl)-pyrrolo[3,2-b]quinoline,
5,6-Dihydro-3-methyl-N-(3-pyridyl)-furo[3,2-f]indole-7-carboxamide,
2,2-Dimethyl-2,3,6,7-tetrahydro-N-(3-pyridyl)furo[2,3-f]indole-5-carboxamide,
2,3,6,7-Tetrahydro-5-(3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
5-Methyl-N-(3-pyridyl)-2,3,5,6,7,8-hexahydro-1H-pyrrolo[2,3-g]quinoline-1-carboxamide,
2,3-Dihydro-7-hydroxy-1-(3-pyridylcarbamoyl)pyrrolo-[2,3-f]indane,
2,3-Dihydro-7-oxo-1-(3-pyridylcarbamoyl)pyrrolo-[2,3-f]indane,
2-Bromo-5,6-dihydro-N-(3-pyridyl)-thieno-[3,2-f]indole-7-carboxamide,
5,6-Dihydro-N-(3-pyridyl)-thieno[3,2-f]-indole-7-carboxamide,
or a pharmaceutically acceptable salt thereof.

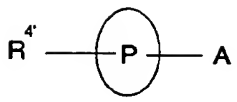
The compounds of the formula (I) can form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric and methanesulphonic.

Certain compounds of formula (I) may also form N-oxides or solvates such as hydrates, and the invention also extends to these forms. When referred to herein, it is understood that the term 'compound of formula (I)' also includes these forms.

Certain compounds of formula (I), for example those where P is pyridyl and $R^4$ is hydroxy or $NR^8R^9$ and at least one of $R^8$ and $R^9$ are hydrogen, may exist tautomerically in more than one form. The invention extends to these and any other tautomeric forms and mixtures thereof.

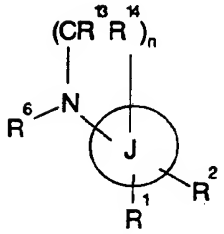
Certain compounds of formula (I) are capable of existing in stereoisomeric forms including enantiomers and the invention extends to each of these stereoisomeric forms and to mixtures thereof including racemates. The different stereoisomeric forms may be separated one from the other by the usual methods, or any given isomer may be obtained by stereospecific or asymmetric synthesis.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises the coupling of a compound of formula (II);



(II)

with a compound of formula (III);



(III)

wherein A and $R^6$ contain the appropriate functional group(s) necessary to form the moiety, $-NR^{5'}CO$ when coupled, wherein $R^{5'}$ is $R^5$ as defined in formula (I) or a group convertible thereto, n, J and P as defined in formula (I), and the variables $R^{1'}$, $R^{2'}$, $R^{4'}$ $R^{13'}$and $R^{14'}$ are $R^1$, $R^2$, $R^4$, $R^{13}$ and $R^{14}$ respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{4'}$, $R^{5'}$, $R^{13'}$ and $R^{14'}$ and when other than $R^1$, $R^2$, $R^4$, $R^5$, $R^{13}$ and $R^{14}$ respectively to $R^1$, $R^2$, $R^4$, $R^5$, $R^{13}$ and $R^{14}$, interconverting $R^1$, $R^2$, $R^4$, $R^5$, $R^{13}$ and $R^{14}$, and forming a pharmaceutically acceptable salt thereof.

Suitable examples of groups A and $R^6$ include:

(i) A is -N=C=O and $R^6$ is -H,

(ii) A is $-NR^{5'}COL$ and $R^6$ is -H,

(iii) A is $-NHR^{5'}$ and $R^6$ is COL, or

(iv) A is halogen and $R^6$ is $-CONHR^{5'}$,

wherein $R^{5'}$ is as defined above and L is a leaving group. Examples of suitable leaving groups L include imidazole, halogen such as chloro or bromo or phenoxy or phenylthio optionally substituted for example with halogen.

When A is -N=C=O and $R^6$ is H the reaction is suitably carried out in an inert solvent for example dichloromethane or toluene at ambient temperature.

When A is $-NR^{5'}COL$ and $R^6$ is H or when A is $-NHR^{5'}$ and $R^6$ is COL, the reaction is suitably carried out in an inert solvent such as dichloromethane at ambient

temperature optionally in the presence of a base, such as triethylamine or in dimethylformamide at ambient or elevated temperature.

When A is halogen and $R^6$ is $CONHR^{5'}$, the reaction is suitably carried out in an inert solvent such as toluene at elevated temperature, optionally in the presence of a base.

Suitable examples of groups $R^{4'}$ which are convertible to $R^4$ alkyl groups include acyl groups which are introduced conventionally and may be converted to the corresponding alkyl group by conventional reduction, such as using sodium borohydride in an inert solvent followed by hydrogenolysis in an inert solvent. Hydrogen substituents may be obtained from alkoxycarbonyl groups which may be converted to hydrogen by hydrolysis and decarboxylation. When $R^4$ is hydroxy it is preferably protected in the compound of formula (II) as, for example, benzyl which is removed by hydrogenation.

Suitable examples of a group $R^{5'}$ which is convertible to $R^5$ include alkoxycarbonyl and benzyl or **para**-methoxybenzyl which are converted to $R^5$ is hydrogen using conventional conditions.

$R^4$ halo and $R^1$/$R^2$ halo groups may be introduced by selective halogenation of the rings P or J respectively using conventional conditions.

Compounds of formula (II) in which A is -N=C=O may be prepared by treating a compound of formula (II) in which :

i) A is amino, with phosgene or a phosgene equivalent, in the presence of excess base in an inert solvent.

ii) A is acylazide (i.e. $CON_3$), via the nitrene, by thermal rearrangement using conventional conditions (ref L.S. Trifonov **et al**, Helv. Chim. Acta 1987 **70** 262).

iii) A is $CONH_2$, via the nitrene intermediate using conventional conditions.

Compounds of formula (II) in which A is $NR^{5'}COL$ can be prepared from the corresponding amine where A is $NR^{5'}H$ by treatment with a phosgene equivalent, for example phenyl chloroformate. Compounds of formula (II) in which A is halogen and $R^{4'}$ is hydrogen are commercially available.

Compounds of formula (III) may be prepared using methods analogous to those well known in the art, for example as disclosed in WO 94/04533.

Novel intermediates of formulae (III) also form part of the invention.

Pharmaceutically acceptable salts may be prepared conventionally by reaction with the appropriate acid or acid derivative. N-oxides may be formed conventionally by reaction with hydrogen peroxide or percarboxylic acids.

Compounds of formula (I) and their pharmaceutically acceptable salts have $5HT_{2C}$ receptor antagonist activity, and certain compounds show $5HT_{2B}$ antagonist activity. Compounds of formula (I) are therefore believed to be of potential use in the treatment of CNS disorders such as anxiety, depression, epilepsy, obsessive compulsive

disorders, migraine, Alzheimers disease, sleep disorders, feeding disorders such as anorexia and bulimia, panic attacks, withdrawal from drug abuse such as cocaine, ethanol, nicotine and benzodiazepines, schizophrenia, and also disorders associated with spinal trauma and/or head injury such as hydrocephalus. Compounds of the invention are also expected to be of use in the treatment of certain GI disorders such as IBS. Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance, in particular in the treatment or prophylaxis of the above disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for the treatment or prophylaxis the above disorders.

The present invention also provides a pharmaceutical composition, which comprises a compound of formula (I) or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or infusable solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colourants.

For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be

dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration.

The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 0.05 to 70.0 mg, for example 0.2 to 5 mg; and such unit doses may be administered more than once a day, for example two or three a day, so that the total daily dosage is in the range of about 0.01 to 100 mg; and such therapy may extend for a number of weeks or months.

When administered in accordance with the invention, no unacceptable toxicological effects are expected with the compounds of the invention.

The following Examples illustrate the preparation of pharmacologically active compounds of the invention.

**Description 1**
**6-Nitro-1-trifluoroacetylindoline (D1)**

6-Nitroindoline (6.50g, 40 mmol) and triethylamine (6.6 ml, 47 mmol) were stirred in dichloromethane (65 ml) as trifluoroacetic anhydride (6.6 ml, 47 mmol) was added dropwise. This mixture was stirred for 0.75h, and water (100 ml) was added. After stirring for 10 min, the mixture was acidified with 5M HCl, and separated. The organic portion was washed with brine, dried ($Na_2SO_4$) and evaporated to give the title compound (9.64g, 93%) as a yellow-brown solid.

NMR ($CDCl_3$) δ : 3.4 (2H, t, J 8), 4.4 (2H, t, J 8), 7.4 (1H, d, J 8), 8.1 (1H, dd, J 8, 2), 9.05 (1H, d, J 2).

**Description 2**
**6-Amino-1-trifluoroacetylindoline (D2)**

6-Nitro-1-trifluoroacetylindoline (D1) (4.10g, 16 mmol) was hydrogenated over 5% palladium on charcoal (60% aqueous paste, 1.0g) in ethanol (200 ml) for 4 h. The catalyst was filtered off, and the filtrate was evaporated to give the title compound (3.60g, 99%) as a light brown solid.

NMR ($CDCl_3$) δ : 3.15 (2H, t, J 8), 3.35 (2H, b), 4.25 (2H, t, J 8), 6.5 (1H, dd, J 8, 2), 7.0 (1H, d, J 8), 7.65 (1H, d, J 2).

**Description 3**
**6-Hydroxy-1-trifluoroacetylindoline (D3)**

6-Amino-1-trifluoroacetylindoline (D2) (2.98g, 13 mmol) was stirred in water (30 ml) as c $H_2SO_4$ (3 ml) was added dropwise. The solution was cooled to 0° C, and $NaNO_2$ (0.98g, 14 mmol) in water (10 ml) was added dropwise, maintaining the temperature ≤ 0° C. The mixture was stirred for 5 min, and then transferred to a boiling solution of $CuSO_4.5H_2O$ (13.0g, 52 mmol) in water (50 ml). The mixture was boiled for 5 min and cooled, and the black solid was filtered off and air-dried. Chromatography on silica gel, eluting with 0-5% methanol in chloroform, gave the title compound (1.01g, 67%) as a dark brown solid.

NMR (DMSO-$d_6$) δ : 3.1 (2H, t, J 8), 4.25 (2H, t, J 8), 6.6 (1H, dd, J 8, 2), 7.1 (1H, d, J 8), 7.6 (1H, d, 2), 9.05 (1H, s).

**Description 4**

**6-(2-Oxopropoxy)-1-trifluoroacetylindoline (D4)**

6-Hydroxy-1-trifluoroacetylindoline (D3) (2.00g, 8.7 mmol), anhydrous $K_2CO_3$ (1.79g, 13.0 mmol) and chloroacetone (0.84 ml, 10.4 mmol) were stirred in dry DMF (20 ml) for 64 h. The mixture was diluted with ethyl acetate (200 ml), washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound (2.42g, 97%) as a brown oil.

Purification of a small portion by chromatography on silica gel, eluting with 0-10% ethyl acetate in chloroform, gave the compound as an off-white solid.

NMR ($CDCl_3$) δ : 2.3 (3H, s), 3.2 (2H, t, J 8), 4.3 (2H, t, J 8), 4.6 (2H, s), 6.75 (1H, dd, J 8, 2), 7.15 (1h, d, J 8), 7.85 (1H, d, J 2).

**Description 5**

**5,6-Dihydro-3-methyl-7-trifluoroacetylfuro[3,2-f]indole (D5)**

c. $H_2SO_4$ (25 ml) was added at 0° C to 6-(2-oxopropoxy)-1-trifluoroacetylindoline (D4) (2.42g, 8.4 mmol). The dark mixture was then stirred at ambient temperature for 15 min, and poured onto ice. The crude product was extracted into ethyl acetate, and the extract was washed with water and brine, dried ($Na_2SO_4$) and evaporated to a brown gum. Chromatography on silica gel, eluting with chloroform, gave the title compound (0.47g, 21%) as a yellow solid.

NMR ($CDCl_3$) δ : 2.25 (3H, s), 3.35 (2H, t, J 8), 4.35 (2H, t, J 8), 7.35 (1H, s), 7.45 (1H, s), 8.35 (1H, s).

**Description 6**

**5,6-Dihydro-3-methylfuro[3,2-f]indole (D6)**

5,6-Dihydro-3-methyl-7-trifluoroacetylfuro[3,2-f]indole (D5) (0.49g, 1.8 mmol) was stirred in ethanol (10 ml) as 2.5M sodium hydroxide (1 ml) was added. The mixture was stirred for 15 min, diluted with water, and extracted with ethyl acetate. The extract was washed with brine, dried ($Na_2SO_4$) and evaporated to give the title compound (0.29g, 96%) as a brown oil.

NMR ($CDCl_3$) δ : 2.2 (3H, s), 3.1 (2H, t, J 8), 3.3 (1H, v b), 3.6 (2H, t, J 8), 6.7 (1H, s), 7.2 (2H, m).

**Description 7**

**5-Benzyloxyindoline (D7)**

5-Benzyloxyindole (14.0g, 63 mmol) was stirred in glacial acetic acid at 15°C as sodium cyanoborohydride (11.9g, 189 mmol) was added portionwise over 1h. The mixture was stirred for a further 1h, poured into water (500 ml) and basified by addition of potassium hydroxide. This mixture was extracted with ethyl acetate, and the extract was dried ($Na_2SO_4$) and evaporated to give the title compound (14.09g, 100%) as a cloudy oil.

$^1H$ NMR (250MHz, $CDCl_3$) δ: 2.99 (2H, t, J8), 3.0 (1H, b), 3.54 (2H, t, J8), 4.98 (2H, s), 6.55 - 6.7 (2H, m), 6.85 (1H, m), 7.3 - 7.5 (5H, m).

**Description 8**

**5-Benzyloxy-1-trifluoroacetylindoline (D8)**

5-Benzyloxyindoline (D7, 14.09g, 63 mmol) and triethylamine (10.5ml, 75 mmol) were stirred in dichloromethane (250ml) as trifluoroacetic anhydride (10.5 ml, 75 mmol) was cautiously added. After stirring for 1h, water (200ml) was added, and the mixture stirred vigorously for 15min, acidified (5M HCl) and separated. The aqueous portion was extracted with dichloromethane, and the combined organics were washed with brine, dried ($Na_2SO_4$) and evaporated to give the title compound (22.5g) as a brown solid.

$^1H$ NMR (250MHz, $CDCl_3$) δ: 3.22 (2H, t, J8), 4.29 (2H, t, J8), 5.07 (2H, s), 6.8 - 6.95 (2H, m), 7.3 - 7.5 (5H, m), 8.12 (1H, d, J8)

**Description 9**

**5-Hydroxy-1-trifluoroacetylindoline (D9)**

5-Benzyloxy-1-trifluoroacetylindoline (D8, 22.5g, notionally 70 mmol) and 5% palladium on charcoal (60% aqueous paste, 5.0g) were hydrogenated in ethanol (400ml) for 18h. A further portion of catalyst was added, and hydrogenation continued for a further 18h. Catalyst was then filtered off onto kieselguhr, and the filtrate was evaporated to a gummy solid. This was dissolved in ethyl acetate, washed successively with dilute HCl, water,

saturated $NaHCO_3$ solution and brine, dried ($Na_2SO_4$) and evaporated to give the title compound (14.37g, 88%) as a light yellow solid.

$^1H$ NMR (200MHz, $CDCl_3/d_6DMSO$) δ: 2.97 (2H, t, J8), 4.01 (2H, t, J8), 6.4 - 6.6 (2H, m), 7.74 (1H, d, J8), 8.8 (1H, b)

**Description 10**
**5-(2-Methyl-1-propen-3-yloxy)-1-trifluoroacetylindoline (D10)**

5-Hydroxy-1-trifluoroacetylindoline (D9, 4.56g, 20 mmol), anhydrous potassium carbonate (4.1g, 30 mmol) and methallyl chloride (3.9ml, 40 mmol) were stirred in dry DMF at 60° C for 16 h. Further aliquots of potassium carbonate and methallyl chloride were then added, and reaction continued for a further 24h. The mixture was then partitioned between ethyl acetate and water, and separated. The organic portion was washed with water and brine, dried ($Na_2SO_4$) and evaporated to give the title compound (5.00g, 89%) as a brown oil.

$^1H$ NMR (250MHz, $CDCl_3$) δ: 1.73 (3H, s), 3.32 (2H, t, J8), 4.26 (2H, t, J8), 4.43 (2H, s), 5.00 (1H, s), 5.09 (1H, s), 6.8 (2H, m), 8.10 (1H, d, J8).

**Description 11**
**2,2-Dimethyl-2,3,6,7-tetrahydro-5-trifluoroacetylfuro[2,3-f]indole (D11)**

5-(2-Methyl-1-propen-3-yloxy)-1-trifluoroacetylindoline (D10, 5.00g, 18 mmol) was stirred under Ar at 215°C in N,N-diethylaniline (25ml) for 5.5h. The mixture was then cooled, diluted with ethyl acetate, washed with 5M HCl and brine, dried ($Na_2SO_4$) and evaporated to give a brown gum. Chromatography on silica (0→100% $CH_2Cl_2/CHCl_3$, gradient) gave the title compound (2.1g, 42%) as a light yellow waxy solid.

$^1H$ NMR (250MHz, $CDCl_3$) δ: 1.48 (6H, s), 3.00 (2H, s), 3.19 (2H, t, J8), 4.25 (2H, t, J8), 6.63 (1H, s), 8.03 (1H, s).

**Description 12**
**2,2-Dimethyl-2,3,6,7-tetrahydrofuro[2,3-f]indole (D12)**

2,2-Dimethyl-2,3,6,7-tetrahydro-1-trifluoroacetylfuro[2,3-f]indole (D11, 0.26g, 0.91 mmol) was stirred in ethanol (10ml) containing 10% sodium hydroxide solution (1ml) for 2h. The mixture was then partitioned between ethyl acetate and water, and separated. The organic

portion was washed with brine, dried ($Na_2SO_4$) and evaporated to give the title compound (0.15g, 85%) as a yellow green oil.

$^1H$ NMR (250MHz, $CDCl_3$) δ: 1.46 (6H, s), 2.92 (2H, s), 2.95 (2H, t, J8), 3.4 (1H, b), 3.50 (2H, t, J8), 6.49 (1H, s), 6.56 (1H, s)

**Description 13**
**2,3,6,7-Tetrahydro-5H-thieno[2,3-f]indole (D13)**

Trifluoroacetic acid (4ml) was added to a mixture of 6,7-dihydro-5-(3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole (Reference WO 94/22871) (1.0g) and triethylsilane (1.63ml), with heating at 50°C. After 140h, the cooled mixture was neutralised with aqueous sodium carbonate solution and the aqueous layer extracted with diethyl ether. The organic phase was dried ($Na_2SO_4$), and concentrated under reduced pressure. The residue was chromatographed on silica eluting with 1% ethanol and chloroform to afford title compound (340mg).

$^1H$ NMR ($CDCl_3$, 250MHz) δ: 2.95 (t, 2H), 3.12 (t, 2H), 3.33 (t, 2H), 3.55 (t, 2H), 6.58 (s, 1H), 6.96 (s, 1H)

**Description 14**
**2,3-Dihydro-1H-pyrrolo[3,2-b]quinoline (D14)**

A solution of ethyl 3-oxopyrrolidine-1-carboxylate (1.0g), 2-amino benzaldehyde (1.0g) and 85% aq sodium hydroxide (2.8ml) in ethanol (20ml) was stirred under an inert atmosphere for 20h. The ethanol was concentrated *in vacuo* and the residue partitioned between chloroform and water. The aqueous layer was acidified to pH8 and extracted with chloroform. The organic phase was dried ($Na_2SO_4$) and concentrated to afford product (950mg).

$^1H$ NMR ($CDCl_3$ 250MHz) δ: 3.50 (t, 2H), 3.95 (t, 2H), 7.15 (s, 1H), 7.51 - 7.60 (m, 2H), 7.71 - 7.78 (m, 1H), 8.04 - 8.10 (m, 1H)

**Description 15**
**6-Trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D15)**

6-Trifluoroacetamidoquinoline (16.5g, 69 mmoles) in methanol (250ml) was treated with nickel chloride hexahydrate (3.3g, 14 mmoles) and sodium borohydride (13.4g, 350 mmoles) portionwise. After 1½ hrs the mixture was concentrated *in vacuo* and the residue treated with dilute hydrochloric acid (500ml). Basification followed by extraction with dichloromethane and chromatography on silica gel gave the title compound (D15) (6.5g, 39%)

NMR ($CDCl_3$) δ: 1.85 - 2.02 (2H, m), 2.71 - 2.85 (2H, m), 3.25 - 3.39 (2H, m), 3.80 - 4.02 (1H, brs), 6.45 (1H, d, J=11Hz), 7.03 - 7.12 (1H, m), 7.15 (1H, s), 7.55 - 7.85 (1H, brs).

**Description 16**
**1-Ethoxycarbonyl-6-trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D16)**

6-Trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D15) (5.2g, 21 m moles) was treated with ethyl chloroformate and triethylamine in the usual way to give the title compound (D16) (6.5g, 96%).

NMR ($CDCl_3$) δ: 1.33 (3H, t, J=9Hz), 1.95 (2H, t, J=7H), 2.78 (2H, t, J=7Hz), 3.75 (2H, t, J=7Hz), 4.25 (2H, q, J=7Hz), 7.15 - 7.22 (1H, m), 7.45 (1H, s), 7.75 (1H, d, J=12Hz), 7.80 - 8.00 (1H, brs)

**Description 17**
**6-Amino-1-ethoxycarbonyl-1,2,3,4,-tetrahydroquinoline (D17)**

Hydrolysis of 1-ethoxycarbonyl-6-trifluoroacetamido-1,2,3,4-tetrahydroquinoline (D16) (6.5g, 20 m moles) with 1.2 equivalents of sodium hydroxide in ethanol gives the title compound (D17) (3.6g, 80%)

NMR ($CDCl_3$) δ: 1.30 (3H, t, J=7Hz), 1.83 - 1.99 (2H, m), 2.70 (2H, t, J=7Hz), 3.40 - 3.60 (2H, brs), 3.71 (2H, t, J=7Hz), 4.21 (2H, q, J=7Hz), 6.38 - 6.57 (2H, m), 7.45 (1H, d, J=10Hz)

**Description 18**

**6-(2,2-Dimethoxyethyl)amino-1-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline (D18)**

6-Amino-1-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline (D17) (3.6g, 16m moles) was hydrogenated over 10% palladium on charcoal catalyst (0.5g) in the presence of dimethoxy ethanal - 41% solution in methyl-t-butyl ether (6.7g, 27m moles) for 4hrs. The catalyst was then filtered off and the filtrate evaporated to dryness. Chromatography on silica gel eluting with 0-2% methanol/dichloromethane gave the title compound (D18) (4.5g, 90%).

NMR ($CDCl_3$) δ: 1.30 (3H, t, J=8Hz), 1.83 - 1.99 (2H, m), 2.70 (2H, t, J=7Hz, 3.20 (2H, d, J=7Hz), 3.39 (6H, s), 3.72 (2H, t, J=7Hz), 4.21 (2H, q, J=8Hz), 4.55 (1H, t, J=6Hz), 6.33 - 6.51 (2H, m), 7.42 (1H, d, J=8Hz).

**Description 19**

**5-Ethoxycarbonyl-1-trifluoroacetyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D19)**

6(2,2-Dimethoxyethyl)amino-1-ethoxycarbonyl-1,2,3,4-tetrahydroquinoline (D18) (4.5g, 15 mmoles) was heated under reflux in a mixture of trifluoroacetic acid (50ml) and trifluroacetic anhydride (20ml) for 60 hrs. The mixture was then evaporated to dryness. Column chromatography on silica gel eluting with 0 - 1% methanol/dichloromethane gave the title compound (D19) (1.65g, 33%)

NMR ($CDCl_3$) δ: 1.32 (3H, t, J=8), 1.92 - 2.12 (2H, m), 2.92 (2H, t, J=7Hz), 3.79 (2H, t, J=7Hz), 4.25 (2H, q, J=8Hz), 6.70 (1H, d, J=5Hz), 7.35-7.42 (1H, m), 7.92 (1H, s), 8.13 (1H, s).

**Description 20**

**5-Ethoxycarbonyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D20)**

5-Ethoxycarbonyl-1-trifluoroacetyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D19) (1.65g, 5m moles) in methanol (50ml) was treated with potassium carbonate (0.9g, 7 m moles) at ambient temperature for 2hrs. The mixture was evaporated to dryness and the residue partitioned between 2% methanol/dichloromethane and water. The organics were dried ($Na_2SO_4$) and evaporated to dryness to give the title compound (D20) (1.05g, 88%).

NMR ($CDCl_3$) δ:1.35 (3H, t, J=8Hz), 1.91 - 2.12 (2H, m), 2.81 (2H, t, J=7Hz), 3.80 (2H, t, J=7Hz), 4.25 (2H, q, J=8Hz), 6.45 - 6.50 (1H, m), 7.05 - 7.15 (2H, m), 7.80 (1H, s), 8.01 - 8.15 (1H, brs)

**Description 21**
**5-Ethoxycarbonyl-2,3,5,6,7,8-hexahydro-1H-pyrrolo[2,3-g]quinoline (D21)**

5-Ethoxycarbonyl-5,6,7,8-tetrahydro-1H-pyrrolo[2,3-g]quinoline (D20) (1.05g, 4 mmoles) in glacial acetic acid (25ml) was treated with sodium cyanoborohydride (1.25g, 20m moles) at ambient temperature for 1hr. The mixture was diluted with water, basified with sodium hydroxide and extracted with dichloromethane. The organics were dried ($Na_2SO_4$) and evaporated to dryness. Chromatography on silica gel eluting with 0 - 2% methanol/dichloromethane gave the title compound (D21) (0.84g, 79%).

NMR ($CDCl_3$) δ:1.32 (3H, t, J=8Hz), 1.85 - 1.98 (2H, m), 2.68 (2H, t, J=7Hz), 2.99 (2H, t, J=9Hz), 3.51 (2H, t, J=9Hz), 3.68 (2H, t, J=7Hz), 4.20 (2H, q, J=8Hz), 6.33 (1H, s), 7.21 (1H, s), 7.30 - 7.42 (1H, brs).

**Description 22**
**5-Methyl-2,3,5,6,7,8-hexahydro-1H-pyrrolo[2,3-g]quinoline (D22)**

5-Ethoxycarbonyl-2,3,5,6,7,8-hexahydro-1H-pyrrolo[2,3-g]quinoline (D21) (0.84g, 3 m moles) in dry tetrahydrofuran (50ml) was treated with lithium aluminum hydride (0.27g, 7 m moles) at ambient temperature for 1hr. The usual work up gave the title compound (D22) (0.64g, 100%).

NMR ($CDCl_3$) δ:1.95 - 2.05 (2H, m), 2.71 (2H, t, J=7Hz), 2.80 (3H, s), 2.95 (2H, t, J=9Hz), 3.15 (2H, t, J=7Hz), 3.45 (2H, t, J=9Hz), 6.40 (2H, s), 6.55 (1H, s).

**Description 23**
**1-Acetyl-6-nitroindoline (D23)**

To a stirred solution of 6-nitroindoline (25g, 0.15mmol) in dichloromethane (200ml) and pyridine (14.7ml, 0.18mol) at 0°C was added dropwise acetyl chloride (13ml, 0.18mol). The mixture was stirred for 1hr at 0°C treated with water (100ml) and stirred for a further ½hr. The phases were separated and the organics washed (5N HCl, $H_2O$, brine), dried and concentrated to afford the title compound (31.5g, 100%) as a pale green solid.

$^1$H NMR (250MHz $CDCl_3$) δ: 2.28 (s, 3H), 3.30 (t, 2H), 4.2 (t, 2H), 7.26 (m, 1H), 7.89 (m, 1H), 8.95 (s, 1H).

**Description 24**
**1-Acetyl-6-aminoindoline (D24)**

A suspension of D23 (31g, 150mmol) and 10% Pd/C (2g) in ethanol (700ml) was hydrogentated (50psi, 45°C) for 1hr. The catalyst was filtered and washed (50% $CH_2Cl_2$/MeOH). The filtrate was concentrated to afford the title compound (26.3g, 99%) as brown oil.

$^1$H NMR (250MHz $CDCl_3$) δ: 2.20 (s, 3H), 3.05 (t, 2H), 3.66 (br, 2H), 4.00 (t, 2H), 6.35 (m, 1H), 6.92 (m, 1H), 7.68 (s, 1H)

**Description 25**
**1-Acetyl-6-iodoindoline (D25)**

The title compound was prepared from D24 in 76% yield using modified Sandmeyer conditions.

$^1$H NMR (250MHz) δ: 2.20 (s, 3H), 3.14 (t, 2H), 4.04 (t, 2H) 6.90 (d, 1H), 7.82 (dd, 1H), 8.59 (s, 1H).

**Description 26**
**(1-Acetyl-5-indolinyl)propenoic acid, benzyl ester (D26)**

The title compound was prepared from D25 and benzyl acrylate using Heck conditions[1] in 70% yield.

$^1$H NMR (250MHz $CDCl_3$) δ: 2.22 (s, 3H), 3.20 (t, 2H), 4.10 (t, 2H), 5.24 (s, 2H), 6.39 (d, 1H), 7.37 (m, 7H), 7.68 (d, 1H), 8.20 (d, 1H).

[1]Organic reactions, Vol. 27, pg 345-390.

**Description 27**
**(1-Acetyl-5-indolinyl)propionic acid (D27)**

The title compound was prepared from D26 using standard hydrogenation conditions in 92% yield as a white solid.

**Description 28**
**1-Acetyl-2,3-dihydro-7-oxo pyrrolo [2,3-f]indane (D28)**

A solution of D27 (6.2g, 26.6 mmol) in dichloromethane (100ml) was treated with oxalyl chloride (2.48ml, 29mmol) and dimethylformamide (2ml, dropwise) and stirred for 20 minutes. The solvent was removed under reduced pressure and the residue dissolved in dichloromethane (100ml) and cooled to 0°C. To this solution was added portionwise aluminium chloride (10.6g, 79mmol) and the mixture allowed to warm to room temperature and stirred for 12 hours. The mixture was poured onto ice and 5N HCl (50ml) added. The aqueous was extracted (dichloromethane) and the organics dried and concentrated. Flash chromatography on the residue eluting with 50% ethyl acetate/60°C-80°C petroleum ether afforded the title compound (4.1g, 72%) as a white solid.

$^1$H NMR (250MHz $CDCl_3$) δ: 2.24 (s, 3H), 2.70 (m, 2H), 3.07 (m, 2H), 3.25 (t, 2H),4.12 (t, 2H), 7.24 (s, 1H), 8.49 (s, 1H).

**Description 29**
**Acetyl-2,3-dihydro-7-hydroxy-pyrrolo-[2,3-f]indane (D29)**

To a stirred suspension of D28 (2.9g, 13mmol) in ethanol (100ml) was added portionwise sodium borohydride (0.6g, 15mmol) under argon. The suspension was stirred at room temperature for 4 days and the solvent removed *in vacuo*. The residue was triturated with water. Filtration and drying of the solid afforded the title compound (2.6g, 92%) as a white solid.

$^1$H NMR (250MHz, $CDCl_3$) δ: 1.9 (m, 1H), 2.48 (m, 1H), 2.71 (m, 1H), 2.95 (m, 3H), 3.52 (t, 2H), 4.82 (br, 1H), 5.10 (t, 1H), 6.68 (s, 1H), 6.99 (s, 1H).

**Description 30**

**2,3-Dihydro-7-hydroxy-pyrrolo-[2,3-f]-indane (D30)**

A suspension of D29 (1g, 4.6mmol) in ethanol (30ml) was treated with 10% N sodium hydroxide solution (20ml) and sodium hydroxide pellets (1.1g, 27.5mmol). The mixture was refluxed for 12 hours under argon, cooled and partitioned between dichloromethane and water. The organic phase was dried and concentrated to give the title compound (0.29g, 37%) as a yellow solid.

$^1$H NMR (250MHz $CDCl_3$) δ: 1.9 (m, 1H), 2.45 (m, 1H), 2.70 (m, 1H), 2.94 (m, 3H) 3.53 (t, 2H), 5.11 (t, 1H), 6.68 (s, 1H), 7.0 (s, 1H)

**Description 31**

**1,1'-Diacetyl-(6-indolyl)-disulphide (D31)**

N-methyl-6-(chlorosulphonyl)indoline[1] was converted to the title compound in 50% yield using the method of Olah *et al*[2].

**References**

1. Carlier, P.R., Lockshin, M.P., Filosa, M.P., *J. Org. Chem.*, 1994, 59, 3232.
2. Olah, G.A., Navang, S.C., Field, L.A., Salem, G.F., *J. Org. Chem.*, 1980, 45, 4792.

**Description 32**

**1-Acetyl-6-mercaptoindoline (D32)**

A mixture of (1,1'-diacetyl-(6-indolyl)-disulphide) (2.76g, 7.2 mmol) triphenyl phosphine (2.8g, 10.8 mmol) and concentrated hydrochloric acid (20 drops) in dioxane/water (100ml/ 10ml) was heated to reflux under argon for 2 h. The mixture was evaporated to dryness, redissolved in ethyl acetate and extracted (2x) with 1% aqueous sodium hydroxide. The aqueous extract was washed with ethyl acetate, then acidified with 1M aqueous hydrochloric acid and extracted (2x) with ethyl acetate. Drying (sodium sulphate) and evaporation afforded the product as a white solid (1.36g, 49%).

NMR ($CDCl_3$): 2.20 (3H, s), 3.15 (2H, t, J 8Hz), 3.50 (1H, s), 4.05 (2H, t, J 8Hz), 6.90 (1H, dd, J 6Hz), 7.05 (1H, d, J 6Hz) and 8.15 (1H, d, J 1Hz)

**Description 33**
**1-Acetyl-6-(2,2-diethoxyethylthio)-indoline (D33)**

A solution of 1-acetyl-6-mercaptoindoline (4.25g, 22 mmol) in DMF (30 ml) at 0° C under argon was treated with sodium hydride (0.7g, 80% dispersion, 0.55g of NaH, 23 mmol) then after 0.75h with the bromoacetaldehyde diethyl acetal (4ml, 5.1g, 26.4 mmol). The mixture was heated to 50° C for 1 h, then aqueous ammonium chloride (10 ml) was added and the mixture evaporated to dryness. The residue was dissolved in ethyl acetate and washed with dilute brine (3x), brine (1x), then dried ($Na_2SO_4$) and evaporated. Chromatography on silica, eluting with a 0-2% methanol in dichloromethane gradient afforded the product as a colourless oil (4.4g, 65%).

**Description 34**
**7-Acetyl-5,6-dihydro-7H-thieno[3,2-f]indole (D34)**

A solution of 1-acetyl-6-(2,2-diethoxyethylthio)indoline (0.42g, 1.35 mmol) in toluene (8 ml) was treated with a solution of titanium tetrachloride in toluene (1M; 1.6 ml, 1.6 mmol) and heated to 50° C for 10 minutes. The cooled reaction mixture was partitioned between ethyl acetate and aqueous sodium bicarbonate. The organic extract was dried ($Na_2SO_4$) and evaporated affording a brown oil (0.24g). Chromatography, eluting with 50%, 70%, then 100% ethyl acetate in 60/80 petroleum ether afforded the title compound as a white solid (100 mg, 33%).

NMR ($CDCl_3$) δ:2.25 (3H, s), 3.30 (2H, t, J8Hz), 4.10 (2H, t, J8Hz), 7.30 (1H, d, J5Hz), 7.45 (1H, d, J5Hz), 7.60 (1H, s), 8.65 (1H, s).

**Description 35**
**7-Acetyl-2-bromo-5,6-dihydro-7H-thieno[3,2-f]indole (D35)**

A solution of the 7-acetyl-5,6-dihydro-7H-thieno[3,2-f]indole (90 mg, 0.41 mmol) in chloroform (6 ml) was treated with a solution of bromine (100 mg, 0.62 mmol) in chloroform (1 ml). After 0.75h the reaction mixture was diluted with chloroform (20 ml), and washed with dilute aqueous sodium sulphite, then half-saturated brine. Drying ($Na_2SO_4$) and evaporation afforded a white solid (130 mg). Chromatography, on silica, eluting with 0-100% ethyl acetate in 60/80 petroleum ether afforded the product as a white crystalline solid (108 mg, 83%).

NMR ($CDCl_3$) δ:2.25 (3H, s), 3.25 (2H, q, J 8Hz), 4.10 (2H, q, J 8Hz), 7.15 (1H, s), 7.40 (1H, s), 8.60 (1H, s).

**Description 36**

**2-Bromo-5,6-dihydro-7H-thieno[3,2-f]indole (D36)**

This was prepared from D35 using a similar method to D12 affording the title compound as a white solid (125mg, 67%).

NMR ($CDCl_3$) δ:3.10 (2H, t, J 8Hz), 3.60 (2H, t, J 8Hz), 3.90 (1H, bs), 6.85 (1H, s), 7.10 (1H, s), 7.45 (1H, s).

**Description 37**

**5,6-Dihydro-7H-thieno[3,2-f]indole (D37)**

This was prepared from D34 using a similar method to D12 affording the title compound as a white solid (40 mg, 60%).

NMR ($CDCl_3$) δ:3.10 (2H, t, J 8Hz), 3.60 (2H, t, J 8Hz), 3.90 (H, bs), 7.05 (1H, s), 7.10 (d, J5Hz), 7.15 (d, J5Hz), 7.50 (1H, s).

**Example 1**

**1-(3-Pyridylcarbamoyl)-2,3-dihydro-1H-pyrrolo [2,3-g] quinoline (E1)**

A solution of nicotinoyl azide (90 mg, 0.6 mmol) in toluene (4 ml) was heated under reflux for 1.75 h. After cooling, a solution of 2,3-dihydro-1H-pyrrolo [2,3-g] quinoline (0.1g, 0.59 mmol) in dichloromethane was added and the mixture was stirred overnight. The precipitate was filtered off and washed with petrol. Recrystallisation from dichloromethane/petrol gave the title compound (0.09g, 53%), m.p. 215-216° C.

NMR ($d_6$-DMSO) δ : 3.43 (2H, t, J = 7), 4.27 (2H, t, J = 7), 7.39 (2H, m), 7.80 (1H, s), 8.04 (1H, d, J = 8), 8.23 (1H, d, J = 8), 8.28 (2H, s), 8.69 (1H, m), 8.81 (1H, s), 8.92 (1H, s).

**Example 2**

**2-Methyl-6,7-dihydro-5-(3-pyridylcarbamoyl)-furo[2,3-f]indole (E2)**

This was prepared from 2-methyl-6,7-dihydrofuro[2,3-f]indole (0.18g, 1.0 mmol) and nicotinoyl azide (0.17g, 1.1 mmol), following the procedure of Example 1. The reaction mixture was evaporated to dryness, and chromatographed on silica gel, using 0-4% methanol/chloroform. The product was triturated with toluene and dried *in vacuo* to give the title compound (0.18g, 59%) as a white powder, m.p. 230-230.5° C.

NMR (DMSO-$d_6$) δ : 2.4 (3H, s), 3.25 (2H, t, J = 8), 4.2 (2H, t, J = 8), 6.5 (1H, s), 7.3 (2H, m), 8.0 (2H, m), 8.2 (1H, d, J = 4), 8.7 (1H, s), 8.75 (1H, s).
m.s. (m/z): Found, M+1 = 294. $C_{17}H_{15}N_3O_2$ requires M + 1 = 294
Analysis: Found: C, 69.5; H, 5.3; N, 14.3%.
$C_{17}H_{15}N_3O_2$ requires C, 69.6; H, 5.2; N, 14.3%.

**Example 3**

**1-(3-Pyridylcarbamoyl)-2,3-dihydropyrrolo-[2,3-f]-indene (E3)**

A solution of 3-pyridylisocyanate (prepared by heating nicotinoyl azide 0.32g, 2.1 mmol) in toluene was added to a stirred solution of 2,3-dihydropyrrolo-[2,3-f]indene (0.31g, 1.9 mmol) in dichloromethane. After 24 hr stirring, the solid was filtered and chromatographed to yield the title compound 0.42g, 80% as a tan powder.

NMR (250 MHz, DMSO) δ = 8.85 (m, 1H Ar): 8.77 (s, 1H, Ar), 8.31 (d, 1H, J = 5, Ar), 8.10 (m, 2H, Ar), 7.38 (m, 2H, Ar), 6.95 (dd, 1H, J = 5, alkene), 6.61 (dd, 1H, J = 5, alkene), 4.28 (t, 2H, J = 7, indoline), 3.3 (t, 2H, J = 7.5, indoline)
Mpt. = 180° -182° C (dec.)

**Example 4**

**2,3-Dihydro-1-(3-pyridylcarbamoyl)-pyrrolo[3,2-b]quinoline (E4)**

A solution of nicotinoyl azide (218 mg) in dry toluene (5 ml) was heated at reflux for 5 min, cooled to r.t. and poured into a solution of 2,3-dihydro-pyrrolo[3,2-b]quinoline (250 mg) in dichloromethane (5 ml). The mixture was cooled for 2h and the product removed by filtration. Column chromatography on silica using chloroform and increasing volumes of ethanol (up to 20%) as eluant and subsequent crystallisation from ethanol-diethyl ether gave the title compound as a beige solid (50 mg).

$^1$H NMR ($d_6$-DMSO, 270 MHz) δ : 3.44 (t, 2H), 4.28 (t, 2H), 7.38 (dd, 1H), 7.41-7.59 (m, 2H), 7.85 (d, 2H), 7.99-8.08 (m, 1H), 8.27 (dd, 1H), 8.41 (s, 1H), 8.81 (d, 1H), 8.99 (b s, 1H).

m.p. 205-208° C

$M^+$ (EI) 290

**Example 5**

**5,6-Dihydro-3-methyl-N-(3-pyridyl)-furo[3,2-f]indole-7-carboxamide (E5)**

Nicotinoyl azide (0.14g, 0.94 mmol) was stirred at reflux under Ar in dry toluene (5 ml) for 0.75h, and cooled to ambient temperature. This was then filtered through cotton wool into a stirred solution of 5,6-dihydro-3-methylfuro[3,2-f]indole (D6) (0.15g, 0.86 mmol) in dichloromethane (5 ml). After stirring for 15 min, the suspension was cooled in ice, and the precipitate was filtered off and dried. This gave the title compound (0.15g, 59%) as a tan powder.

NMR (DMSO-$d_6$) δ : 2.17 (3H, s), 3.27 (2H, t, J 8), 4.24 (2H, t, J 8), 7.35 (2H, m), 7.62 (1H, d, J 2), 8.01 (2H, m), 8.24 (1H, m), 8.76 (2H, s).

M.S. (C.I.) (m/z) $[M + H]^+ = 294$. $C_{17}H_{15}N_3O_2$ requires $[M + H]^+ = 294$

**Example 6**

**2,2-Dimethyl-2,3,6,7-tetrahydro-N-(3-pyridyl)furo[2,3-f]indole-5-carboxamide (E6)**

This material was prepared from 2,2-dimethyl-2,3,6,7-tetrahydrofuro[2,3-f]indole (D12, 0.147g, 0.77mmol), following the procedure of Example 1. This gave the title compound (0.147g, 61%) as a white powder.

$^1$H NMR (250MHz, $CDCl_3$) δ: 1.48 (6H, s), 2.99 (2H, s), 3.18 (2H, t, J8), 4.11 (2H, t, J8), 6.60 (2H, s), 7.15 - 7.30 (2H, m), 7,76 (1H, s), 8.08 (1H, m), 8.30 (1H,d, J4), 8.50 (1H, d, J2).

**Example 7**

**2,3,6,7-Tetrahydro-5-(3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole (E7)**

A solution of nicotinoyl azide (309mg) in toluene (5ml) was heated to reflux for 5 min and cooled to room temperature and poured into a solution of 2,3,6,7-tetrahydro-5H-

thieno[2,3-f]indole D13 (340mg) in $CH_2Cl_2$ (20ml). After 2h at 0°C, the product was collected by suction filtration and recrystallised from ethanol/$CH_2Cl_2$ to give the title compound as a white powder (280mg).

m.p. 185-189°C

H NMR ($CDCl_3$, 250MHz)δ: 3.16 - 3.30 (4H, m), 3.40 (t, 2H), 4.12 (t, 2H), 6.44 (s, 1H), 7.02 (s, 1H), 7.23 - 7.30 (m, 1H), 7.82 (s, 1H), 8.10 (dd, 1H), 8.35 (d, 1H), 8.50 (d, 1H)

**Example 8**

**5-Methyl-N-(3-pyridyl)-2,3,5,6,7,8-hexahydro-1H-pyrrolo[2,3-g]quinoline-1-carboxamide hydrogen oxalate salt (E8)**

The title compound was prepared in the usual manner from 5-methyl-2,3,5,6,7,8-hexahydro-1H-pyrrolo-[2,3-g]quinoline (D22) (0.64g, 3m moles) and 3-pyridylisocyanate (0.4g, 3 mmoles) followed by treatment with oxalic acid and recrystallisation from methanol/diethylether. This gave (E8) (0.42g, 31%) m.p.193-194°C

NMR (DMSO-$d_6$) δ: 1.80 - 1.95 (2H, m), 2.68 (2H, t, J=7Hz), 2.79 (3H, s), 3.05 - 3.19 (4H, m), 4.05 (2H, t, J=9Hz), 6.52 (1H, s), 7.30-7.38 (1H, m), 7.49 (1H, s), 7.97 - 8.03 (1H, s), 8.15 - 8.25 (1H, brs), 8.59 (1H, s), 8.71 - 8.83 (1H, brs).

**Example 9**

**2,3-Dihydro-7-hydroxy-1-(3-pyridylcarbamoyl)pyrrolo-[2,3-f]indane (E9)**

A solution of 3-pyridyl acyl azide (0.25g, 1.6mmol) in toluene (10ml) was refluxed under argon for ~½hr and cooled. To a solution of D30 (0.27g, 1.6mmol) in dichloromethane (10ml) was added the freshly formed 3-pyridylisocyanate solution. The solid which precipitated was filtered and dried. Recrystallisation from dichloromethane/ethanol afforded the title compound (0.33g, 70%) as a white solid.

$^1$H NMR (250MHz $d_6$ DMSO) δ: 1.78 (m, 1H), 2.31 (m, 1H), 2.61 (m, 1H) 2.82 (m, 1H), 3.14 (t, 2H), 4.12 (t, 2H), 4.95 (t, 1H), 5.2 (d, 1H), 7.01 (s, 1H),7.32 (m, 1H), 7.89 (s, 1H), 7.98 (dd, 1H),8.20 (m, 1H), 8.66 (s, 1H), 8.75 (m, 1H)

m.p. 200-201°C

$C_{17}H_{17}N_3O_2$ requires C, 69.14; H, 5.80; N, 14.23

Found C, 68.85; H, 5.94; N, 14.34

**Example 10**

**2,3-Dihydro-7-oxo-1-(3-pyridylcarbamoyl)pyrrolo-[2,3-f]indane (E10)**

To a stirred suspension of E9 (0.5g, 1.7mmol) in dichloromethane (20ml) was added manganese dioxide (1.03g, 11.9mmol) and the mixture refluxed for 36 hours under argon. The mixture was filtered through kieselguhr, the pad washed (5% methanol/dichloromethane) and the filtrate concentrated. Flash chromatography eluting with 2% methanol/dichloromethane afforded the title compound (0.23g, 46%) as a white solid.

m.p. >250°C

$^1$H NMR (250MHz $d_6$-DMSO) δ: 2.63 (m, 2H), 3.01 (m, 2H, m), 3.28 (t, 2H), 4.21 (t, 2H), 7.35 (m, 2H), 8.00 (m, 2H), 8.24 (m, 1H), 8.74 (d, 1H), 8.80 (s, 1H)

M.S. $^m/_z$=293 (28%)

$C_{17}H_{15}N_3O_2.H_2O$ requires C, 65.56; H, 5.50; N, 13.96

Found C, 65.55; H, 5.01; N, 13.59

**Example 11**

**2-Bromo-5,6-dihydro-N-(3-pyridyl)-thieno-[3,2-f]indole-7-carboxamide (E11)**

This was prepared from D36 according to the general method as for Example 1 affording the title compound as a white solid (158 mg, 86%) m.p. >200° C.

δ(DMSO): 3.30 (2H, t, J 8Hz), 4.20 (2H, , J 8Hz), 7.35 (1H, m), 7.45 (1H, s), 7.60 (1H, s), 8.00 (1H, m), 8.25 (1H, m), 8.35 (1H, s), 8.75 (1H, m), 8.80 (1H, s).

m/e 375

$M^+$ $C_{16}H_{12}N_3Br$ O S requires 375

**Example 12**

**5,6-Dihydro-N-(3-pyridyl)-thieno[3,2-f]-indole-7-carboxamide (E12)**

This was prepared from D37 by the general method of Example 1 affording the title compound as a white solid (15 mg, 44%), mp 218-22° C.

NMR (DMSO) δ: 3.30 (2H, t, J 8Hz), 4.25 (2H, t, J 8Hz), 7.30 (1H, d, J 5Hz), 7.35 (1H, m), 7.55 (1H, d, J 5Hz), 7.70 (1H, s), 8.00 (1H, m), 8.25 (1H, m), 8.40 (1H, s), 8.80 (2H, m).

m/e 295

$M^+$ $C_{16}H_{13}N_3O$ S requires 295

**Pharmacological Data**

**[$^3$H]-mesulergine binding to rat or human 5-HT$_{2C}$ clones expressed in 293 cells in vitro**

Evidence from the literature suggests that 5-HT$_{2C}$ antagonists may have a number of therapeutic indications including the treatment of anxiety, migraine, depression, feeding disorders and obsessive compulsion disorders. (Curzon and Kennett, 1990; Fozard and Gray, 1989) and Alzheimer's Disease (Lawlor, 1989, J. Arch. Gen. Psychiat. Vol. 46 p.542).

The affinity of test drugs for the 5-HT$_{2C}$ binding site can be determined by assessing their ability to displace [$^3$H]-mesulergine from 5-HT$_{2C}$ clones expressed in 293 cells (Julius *et al.*, 1988). The method employed was similar to that of Pazos et al, 1984.

The cells suspension (400ml) was incubated with [$^3$H]-mesulergine (0.5nM) in Tris HCl buffer (pH 7.4) at 37°C for 30 minutes. Non-specific binding was measured in the presence of mianserin ($10^{-6}$M). Ten concentrations of test drug ($3 \times 10^{-9}$ to $10^{-4}$M final concentration) were added in a volume of 50ml. The total assay volume was 500ml. Incubation was stopped by rapid filtration using a Brandel cell harvester and radioactivity measured by scintillation counting. The $IC_{50}$ values were determined using a four parameter logistic program (DeLean 1978) and the $pK_i$ (the negative logarithm of the inhibition constant) calculated from the Cheng Prusoff equation where:

$$K_i = \frac{IC_{50}}{1 + \frac{C}{Kd}}$$

$K_i$ = inhibition constant.

C = concentration of [$^3$H]-mesulergine

Kd = Affinity of mesulergine for 5-HT$_{2C}$ binding sites.

Curzon, G.A. and Kennett, G.A. (1990). TIPS, Vol. 11, 181-182.

Fozard, J.R. and Gray, J.A. (1989). TIPS, Vol. 10, 307-309.

Pazos, A. *et al.* (1984). Eur. J. Pharmacol., 106, 531-538.

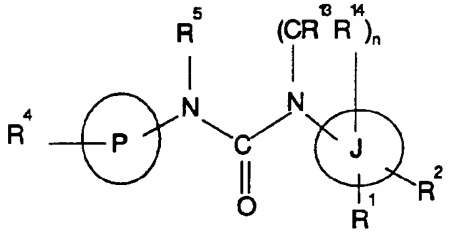
Julius *et al.* (1988) Science 241, 558-564

DeLean A, Munson P.J., Rodbaud D (1978) Am. J. Physiol 235, E97-E102.

The compounds of examples 1 to 12 had pKi values in the range 6.43 - 8.58

**Claims:**

1. A compound of formula (I) or a salt thereof:



(I)

wherein:

P represents phenyl, a quinoline or isoquinoline residue, or a 5- or 6-membered aromatic heterocyclic ring containing up to three heteroatoms selected from nitrogen, oxygen or sulphur;

J represents a bicyclic aromatic or partially saturated ring system;

$R^1$ and $R^2$ are independently hydrogen, halogen, hydroxy, oxygen, or $C_{1-6}$ alkyl optionally substituted by one or more halogen atoms;

$R^4$ is hydrogen, $C_{1-6}$ alkyl, $C_{1-6}$ alkylthio, halogen, nitro, cyano, $CF_3$, $NR^8R^9$, $CO_2R^{12}$, $CONR^{12}$ or $OR^{12}$, where $R^8$, $R^9$ and $R^{12}$ are independently hydrogen, $C_{1-6}$ alkyl or aryl$C_{1-6}$alkyl;

$R^5$ is hydrogen or $C_{1-6}$ alkyl;

n is 2 or 3; and

the groups $R^{13}$ and $R^{14}$ are independently hydrogen or $C_{1-6}$ alkyl,

provided that:

P is not a heterocyclic group when J forms a benzothiophene ring.

2. A compound according to claim 1 in which P is pyridyl.

3. A compound according to claim 2 or 3 in which J is quinoline, tetrahydroquinoline, benzofuran, benzothiophene, or indane.

4. A compound according to any one of claims 1 to 3 in which $R^1$ and $R^2$ are both hydrogen.

5. A compound according to any one of claims 1 to 4 in which $R^4$ and $R^5$ are both hydrogen.

6. A compound according to any one of claims 1 to 5 in which $(CHR^{13})_n$ is an ethylene group.

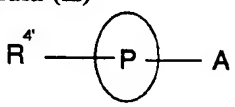
7. A compound according to claim 1 which is selected from:

1-(3-Pyridylcarbamoyl)-2,3-dihydro-1H-pyrrolo [2,3-g] quinoline,
2-Methyl-6,7-dihydro-5-(3-pyridylcarbamoyl)-furo[2,3-f]indole,
1-(3-Pyridylcarbamoyl)-2,3-dihydropyrrolo-[2,3-f]-indene,
2,3-Dihydro-1-(3-pyridylcarbamoyl)-pyrrolo[3,2-b]quinoline,
5,6-Dihydro-3-methyl-N-(3-pyridyl)-furo[3,2-f]indole-7-carboxamide,
2,2-Dimethyl-2,3,6,7-tetrahydro-N-(3-pyridyl)furo[2,3-f]indole-5-carboxamide,
2,3,6,7-Tetrahydro-5-(3-pyridylcarbamoyl)-5H-thieno[2,3-f]indole,
5-Methyl-N-(3-pyridyl)-2,3,5,6,7,8-hexahydro-1H-pyrrolo[2,3-g]quinoline-1-carboxamide,
2,3-Dihydro-7-hydroxy-1-(3-pyridylcarbamoyl)pyrrolo-[2,3-f]indane,
2,3-Dihydro-7-oxo-1-(3-pyridylcarbamoyl)pyrrolo-[2,3-f]indane,
2-Bromo-5,6-dihydro-N-(3-pyridyl)-thieno-[3,2-f]indole-7-carboxamide,
5,6-Dihydro-N-(3-pyridyl)-thieno[3,2-f]-indole-7-carboxamide,
or a pharmaceutically acceptable salt thereof.

8. A compound according to any one of claims 1 to 7 for use in therapy.

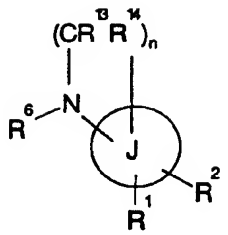
9. A pharmaceutical composition which comprises a compound according to any one of claims 1 to 7 and a pharmaceutically acceptable carrier or excipient.

10. A process for the preparation of a compound of formula (I) or a salt thereof, which process comprises:
the coupling of a compound of formula (II)




(II)

with a compound of formula (III);



(III)

wherein A and $R^6$ contain the appropriate functional group(s) necessary to form the moiety, $-NR^{5'}CO$ when coupled, wherein $R^{5'}$ is $R^5$ as defined in formula (I) or a group convertible thereto, n, J and P as defined in formula (I), and the variables $R^{1'}$, $R^{2'}$, $R^{4'}$ $R^{13'}$and $R^{14'}$ are $R^1$, $R^2$, $R^4$, $R^{13}$ and $R^{14}$ respectively, as defined in formula (I), or groups convertible thereto, and thereafter optionally and as necessary and in any appropriate order, converting any $R^{1'}$, $R^{2'}$, $R^{4'}$, $R^{5'}$, $R^{13'}$ and $R^{14'}$ and when other than $R^1$, $R^2$, $R^4$, $R^5$, $R^{13}$ and $R^{14}$ respectively to $R^1$, $R^2$, $R^4$, $R^5$, $R^{13}$ and $R^{14}$, interconverting $R^1$, $R^2$, $R^4$, $R^5$, $R^{13}$ and $R^{14}$, and forming a pharmaceutically acceptable salt thereof.

# INTERNATIONAL SEARCH REPORT

Int ional Application No
PCT/EP 95/00901

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D471/04 A61K31/33 C07D491/04 C07D209/70 C07D495/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category ° | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | WO,A,94 04533 (SMITHKLINE BEECHAM PLC) 3 March 1994 cited in the application see claims --- | 1,7 |
| P,A | WO,A,94 14801 (SMITHKLINE BEECHAM PLC) 7 July 1994 see claims --- | 1,7 |
| P,X | WO,A,94 22871 (SMITHKLINE BEECHAM PLC) 13 October 1994 see claims ----- | 1,7 |

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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| Date of the actual completion of the international search | Date of mailing of the international search report |
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| 15 May 1995 | 30. 05. 95 |

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# INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ational Application No
PCT/EP 95/00901

| Patent document cited in search report | Publication date | Patent family member(s) | | Publication date |
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| | | CA-A- | 2142721 | 03-03-94 |
| | | CN-A- | 1086819 | 18-05-94 |
| | | SI-A- | 9300438 | 31-03-94 |
| WO-A-9414801 | 07-07-94 | NONE | | |
| WO-A-9422871 | 13-10-94 | NONE | | |